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NANOSUSPENSION SOLIDIFICATION TECHNIQUE: EVALUATION OF HIGH SHEAR GRANULATION AS PER INDUSTRIAL PERSPECTIVE

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ABSTRACT

The nanoparticles for pharmaceutical application are around now for over 35 years, but only few are commercialized. The major hurdle in its effective utilization is lack of basic understanding in nanosuspension solidification techniques. This study evaluates the efficacy of high shear granulation in converting nanosuspension to solid oral dosage form. Nanosuspension was manufactured using a media milling approach and was used as a binder for granulating two different blends containing varying ratios of soluble to insoluble filler. Results obtained by PSD and zeta potential confirmed the required nano characteristics of the nanosuspension. The granules characteristics revealed good flow property of the blends. Results demonstrated that, formulation F02 containing lower ratio of lactose to MCC yielded a tablet with low weight, thickness, disintegration time and similar dissolution rate as compared to formulation F01. The nanoparticulate tablets showed an increased dissolution velocity against the marketed preparation. The quantity and type of filler had no significant impact on the dissolution velocity.

KEYWORDS: Nanosuspension solidification technique, Dissolution velocity, High shear wet granulation, Soluble filler, Insoluble filler

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INTRODUCTION

"Nanoparticles are solid colloidal particles ranging in size from 10 to 1000 nm (1µm)". They consist of macromolecular materials in which the active principle (drug or biologically active material) is dissolved, entrapped, encapsulated and/or to which the active principle is adsorbed or attached[1]. The historical development of nanoparticles started with Paul Ehrlich, attempted for the first time by Ursula Scheffel and extensively worked by the group of Professor Peter Speiser. The research group of Prof. Speisers at first investigated polyacrylic beads for oral [2,3,4] then focused on microcapsules and in the late 1960s developed the first nanoparticles for drug delivery purposes and for vaccines. Nanoparticles are usually produced in liquid media and also stated as nanosuspension. Top-down (attrition) and Bottom-up (molecular deposition) are the two main methods used for manufacture of drug nanoparticles. All the US FDA approved nano technology based products are manufactured by top-down approach (Table 1)[6]. This process involves subjecting the large drug crystals either to high pressure homogenization or high energy wet milling in fluid phase, where the drug is homogenously dispersed in stabilizer mixture. Selection of proper steric and electrostatic stabilizer and its optimum quantity plays a major role in formulating a nanosuspension. The drug nanosuspension can be given by oral route or by intravenous injection. The nanosuspensions usually have the stability issues involved in physical (Ostwald ripening and agglomeration) and chemical (hydrolysis) process. In such cases, solid dosage form is considered more attractive, due to their patient compliance (marketing aspects) and good stability. Therefore, a major challenge in realizing the full commercial potential of nanosizing is the successful conversion of nanosuspension into the solid dosage form. Solidification methods of nanosuspension generally include pelletization, fluid bed granulation, spray drying and lyophilization.

Tuula Ryde et al. in US patent number 7,320,802 described a process to prepare nanoparticulate active composition[7]. The nanosuspension as per this patent was prepared by using top-down technology. This nanosuspension along with additional components was sprayed onto lactose monohydrate in fluid bed coater. This spray granulated intermediate along with extragranular components was further compressed to yield a tablet. The FBC or fluid bed granulator agglomerates finer particles into large granules in a one pot process. In pharmaceutical industry it is mainly used for pelletization, layering of low dose drug and for modified or targeted release coating. The agglomeration process in FBC involves sequential layering of dispersion on the granular excipient with particle size in few hundred microns. Due to which concentration of solids in the dispersion and its rate of spraying is to be optimized properly to avoid over wetting of the excipient. This leads to increase process time and in turn affects the manufacturing cost of the final product. Gary W. Pace et al. in US patent application number 6,6960,84 described a method to prepare nanoparticulate composition using spray drying approach[8]. As per this patent, the nanosuspension prepared was mixed with bulking agent and was subjected to spray drying. The spray dried active component was blended with excipients and compressed to form a tablet. Spray drying holds good application in food and pharmaceutical industry due to its ease of processing approach. But its use is limited to highly viscous, thermo sensitive or sticky materials. Moreover this process is selected when the advantages gained and value of the end product is balanced against the alternative strategy. Similarly Arwinder S. Nagi in his work titled as "Rapamycin formulations for oral administration" utilized spray coating of nanosuspension of active on an inert core as an alternative to FBC and spray drying approach[9]. Spray coating of nanosuspension on inert core approach is again limited to low dose drug and

also needs optimized process to yield precision and accuracy in results.

The nanoparticles for pharmaceutical application are around now for over 35 years, but the first commercial nanosized product (Rapamun®) appeared on the US market in the year 2001, followed by few more till 2005. Although there are many molecules in pipeline, but only few has been commercialized since then. The limitation for this technology to enter in market is mainly the cost involved in it. All the existing approaches to convert nanosuspension to solid oral dosage form are covered under patent[7,8,9]. Moreover this approach either leads to increased production cost, manufacturing time and required expertise to handle these processes (FBC, spray drying and spray coating) in order to achieve the reproducibility in results. There is a need in the art to provide a readily reproducible, cost and time effective method with lots of expertise to handle it. The present invention satisfies this need. There is a need in the art to evaluate efficacy of high shear wet granulation to overcome the issues associated with prior conventional nanosuspension solidification approaches. The present invention also satisfies these needs. A very negligible amount of research work is available in public domain, evaluating high shear granulation as an alternative approach, considering the industrial perspective of nanosuspension solidification technique; which includes the cost and time of manufacturing. The objective of the present research work was to evaluate the efficacy of high shear wet granulation in converting nanosuspension to solid oral dosage form and to study the effect of particle size and diluent on the rate of drug release. Tablet was the solid oral dosage form selected because of its advantage such as convenient handling, stability, flexibility and palatability over the other oral dosage form. The model compound (Meloxicam) an oxicam derivative, is a member of the enolic acid group of NSAIDs with log P of 0.1 in pH 7.4, a pKa of 1.1 and 4.2, half life of ~20 hours and a molecular weight of 351.41 g/mol. Meloxicam is practically insoluble in water. The meloxicam nanosuspension was formulated using top-down approach. This nanosuspension was converted into tablet using high shear granulation method. The in-vitro properties of the nanoparticulate based composition were evaluated against the marketed formulation Mobic® 15 mg tablet.

Table 1
Nanosized product in US market

Trade name/Drug	Nanotechnology	Solidification technology	Launch year
Rapamune/Sirolimus	Top-Down technology	Spray coat/Tablet	2001
Emend/Aprepitant	Top-Down technology	FBC/Capsule	2003
TriCor/Fenofibrate	Top-Down technology	FBC/Tablet	2004
Megace ES/Megestrol acetate	Top-Down technology	Oral suspension	2005
Abraxane/Paclitaxel	Albumin formulation	IV injection	2005
Triglide/Fenofibrate	IDD solubilisation technology	Spray drying /Tablet	2005

MATERIALS AND METHODS

Meloxicam USP (Dr. Reddys Laboratories Limited, Hyderabad, India), Hydroxypropyl methylcellulose (HPMC) 6cps (Samsung fine chemicals Co., LTD. Korea), Sodium lauryl sulphate (SLS) (Stepan Co. USA), Lactose monohydrate (DMV), Microcrystalline cellulose (MCC) (Avicel PH 101®, FMC Biopolymer, Ireland), Crospovidone XL 10® (BASF Corporation, Noth America), Povidone K-30 (ISP, India), Colloidal silicon dioxide (Aerosil 200®), (Evonik Degussa GmBH, Germany), Stearic acid (PMC Biogenix, United states of America) were used for this study. Mobic® 15 mg tablet (Boehringer Ingelheim, Germany) was

used as a reference sample. Purified water USP was used in this study. Analytical grade chemicals were used for HPLC analysis. Nanosuspension Preparation Nanosuspension preparation involves two main steps; the first one is uniform dispersion of drug and stabilizers (Table 2) in dispersion media and second one is particle size reduction in milling chamber. The uniform dispersion of drug (initial particle size d (90)5.0µm) and stabilizer in dispersion media was prepared using Heidolph mixer (Model: RZR2051 Control, Rose Scientific Ltd., Alberta, Canada) operated at 500 rpm. This suspension was loaded in milling chamber of bead mill (Model: Lab Star 1, Netzsch mill, Germany) for particle size reduction. The milling media used for this study was 0.2-mm yttrium-stabilized zirconium beads. The milling operation was performed in a re-circulation mode with the suspension fed at a rate of 100 mL/min. The bead mill was operated at 2563 rpm and for 3 hours and 48 minutes. The formulation and process parameters used for nanosuspension preparation are the optimized one and are selected from our previous study[10]. The temperature of suspension was controlled during milling by circulating cold water through the outer jacket.

Table 2
Formula composition for Meloxicam nanosuspension

Sr.No.	Ingredients	Quantity /batch (g)
1	Meloxicam (USP)	160.0
2	HPMC 6cps	39.0
3	Sodium lauryl sulphate	3.8
4	Purified water	1854.0

(i) Particle Size Measurement

The particle size distribution of nanosuspension was measured using Malvern Zetasizer (Model: ZS200, Malvern Instruments, United kingdom). The analysis was performed in triplicate for each formulation and the average values of volume distribution were reported

***(ii)* Zeta Potential**

The zeta potential of nanosuspension was measured using Malvern Zetasizer (Model: ZS200, Malvern Instruments, United kingdom) at $25^0C \pm 0.5^0C$. The analysis was performed in triplicate for each formulation and the average values of zeta potential were reported.

(iii) Nanosuspension solidification using wet high shear wet granulation

Two different batch compositions F01 and F02 were dispensed (Table 3). Formulation batch number F01 and F02 contains lactose monohydrate: microcrystalline cellulose in 0.8: 0.2 and 0.2: 0.8 respectively. The intra granular excipients were sieved through a 40 mesh (or 590 mm) screen after dispensing. The sieved excipients were transferred into a high shear granulator (Model: BMG, Bohle, Germany). The impeller was turned on to perform dry mixing for 10 min. The nanosuspension was poured to commence granulation. After nanosuspension was added, the powder was mixed for an additional 4 to 5 minutes with impeller (250 rpm) and chopper (1000 rpm) on, to complete the granule formation process. The granules were dried in a fluid bed dryer (Model: TG200, Retsch FBD, Germany) until the required product temperature was achieved and the granule's loss on drying (LOD) was less than 2%. Dried granules were sifted through 24 mesh manually. The sifted granules were blended with extra-granular excipients (sifted through 40 mesh) in an octagonal blender (Model: BOCB05, Bectochem Consultants & Engineers Pvt. Ltd., India) for 10 min and lubricated with stearic acid (sieved through a 60 mesh screen) for 5 minutes. The lubricated blend was compressed with caplet shaped punch of 17.5X7.25 mm dimensions (F01) and round concave punch 9.5 mm (F02) on a 10 station rotary press (Model: SRC I, Smart press, Pacific tools, India) to get meloxicam nanoparticulate tablet equivalent to 15 mg.

Table 3
Formula composition for nanoparticulate based composition for Meloxicam tablet

Sr.No.	Ingredient	F01	F02
		%	%
	Intragranular blend		
1	Lactose monohydrate (Pharmatose 200M)	68.4	16.6
2	Microcrystalline cellulose (Avicel PH101)	17.1	66.4
3	Povidone (PVP K-30)	5.1	5.0
4	Crospovidone XL-10	3.4	3.3
	Nanosuspension (binder)		
5	Meloxicam	2.1	4.0
6	HPMC 6cps	0.5	1.0
7	Sodium lauryl sulphate	0.1	0.1
8	Purified water	q.s.	q.s.
	Extragranular blend		
9	Crospovidone XL-10	1.7	2.1
10	Colloidal silicon dioxide (Aerosil 200)	0.6	0.3
11	Stearic acid	1.0	1.1
Final tablet weight (mg)		700.3	373.8

qs, quantity sufficient, mg, milligram, Qty, quantity, tab, tablet.
Note: Ingredient number 5, 6 and 7 are part of meloxicam nanosuspension.

(iv) Solid state characterization (powder x-ray diffraction)

Initial unmilled suspension of meloxicam and nanosuspension were dried using spray dryer (Model: LU 222, Labultima, Mumbai, India) under following set of condition: inlet temperature, 85^0C; outlet temperature, 60^0C; feed rate, 2.5mL/min; atomization pressure 2 kg/cm^2. The Powder X-ray diffraction (PXRD) pattern of these samples along with tablets of F01, F02 and their placebos was recorded using an X-ray diffractometer (Bruker axs, D8 Advance) with a Cu line as the source of radiation. Standard runs using a 40-kV voltage, a 40-mA current, and a scanning rate of 0.013° min−1 over a 2θ range of 3–45° were used.

(v) Characterization of the granules

The flowability of the lubricated granules of F01 and F02 was characterized by measuring angle of repose, Hausner ratio and Carr's compressibility index. Angle of repose was determined by pouring the granules through a funnel (10 mm diameter orifice) onto a flat surface and measuring the angle between the horizontal and the slope of the heap of granules. Bulk density was calculated by measuring the volume of 10 g granules in a 25 ml cylinder. The cylinder was tapped 100 times until no further reduction in the volume of the granules was observed. Tapped density was calculated using the volume of the granules after tapping. Carr's compressibility index (CI) and Hausner ratio (HR) were determined according to the following formulas respectively

$$CI = \frac{\text{(Tapped density – Bulk density)}}{\text{Tapped density}} \times 100 \quad (1)$$

$$HR = \text{Tapped density – Bulk density)} \quad (2)$$

(vi) Characterization of the tablets

The thickness and hardness of 10 tablets from each batch were determined using a tablet tester (Model: Tablet tester 8M, Dr.Schleuniger, Pharmatron Inc., Swizerland). The friability of the 10 tablets from each batch was determined using a USP Friability tester (Model: EF-1W, Electrolab, India). The disintegration test of the 6 tablets from each batch was determined using

an automated disintegration apparatus (Model: ED-2ALW, Electrolab, India).

(vii) Dissolution test

In-vitro dissolution of six tablets each of formulation F01, F02 and marketed tablet was determined using the USP Type II apparatus (Model: Disso 2000, LABINDIA, India) at 75 rpm paddle speed in 900 mL of phosphate buffer pH 7.5 at 37^0C ± 0.5^0C. At predetermined time intervals (5, 10, 20, 30, 45 and 60 minutes) 10 ml of sample was withdrawn followed by replenishing the blank dissolution medium and analyzing the amount of drug dissolved using HPLC.

(viii) Stability study of meloxicam nanosuspension

The stability study was conducted to ensure the nanosuspension quality during the period of the solidification process. The meloxicam nanosuspension was filled in 10 ml transparent glass vial packed with rubber stopper. These vials were placed in 2-8 ^{0} C and 25^0 C/60 % RH stability chamber and were evaluated for effect of temperature on particle size distribution and zeta potential. The measurements were performed on initial and 5 day sample.

RESULTS AND DISCUSSION

1. Characterization of nanosuspension

Nanosuspensions for oral route are mainly characterized by particle size distribution (PSD), zeta potential, crystalline status, and dissolution velocity. A particle of less than 400nm is considered to be acceptable for a nanosuspension to be administered intravenously[11]. For a physically stable nanosuspension solely stabilized by electrostatic repulsion, a zeta potential of ±30mV is required as a minimum. In the case of a combined electrostatic and steric stabilization, as a rough guide line of ±20mV is sufficient [12]. The crystalline structure of nanosuspension is important for drugs existing in different polymorphic form. The stability and robustness of a nanosuspension is mainly governed by various formulation and process variables. The formulation and process parameters used for meloxicam nanosuspension manufacturing are selected from our previous study. The initial results for the PSD and zeta potential were found to be in line with the optimized formula of the study. This indicates the robustness of nanosuspension formulation. The meloxicam nanosuspension was found to be chemically stable for 5 day at 25^0C/60 % RH and 2-8^0 C (Table 4).

There was no significant change in d(90) and zeta potential value of meloxicam nanosuspension at both storage condition up to 5 days. Moreover no sign of aggregation, sedimentation or ostwald ripening of the nanosuspension was observed during stability study. The initial zeta potential value of meloxicam nanosuspension was -20mV. Zeta potential is the potential at the hydrodynamic shear plane and can be determined from particle mobility under an electric field. The mobility will depend on surface charge and electrolyte concentration and is indicative of the colloidal stability of the nanosuspension. An increase in the absolute value of zeta potential is correlated with a lesser tendency to aggregate or flocculate. For a nanosuspension that contains both electrostatic and steric stabilizer, an absolute zeta potential of ±20mV is sufficient to consider as a stable nanosuspension. Evaluation of changes in physical form such as polymorphic transition or degree of crystallinity was performed using powder X-ray diffraction. In bead milling operation, the drug nanosuspension is prepared by attrition principle, chances of change in physical form of active is more by this method. The powder X-ray diffraction study of spray dried nanosuspension showed no significant shift in the main peaks when compared with initial unmilled drug. The characteristic peaks for milled drug was observed at same 2ɵ value as that of unmilled drug (Fig 1).

Figure 1
XRD pattern of milled and unmilled meloxicam nanosuspensions

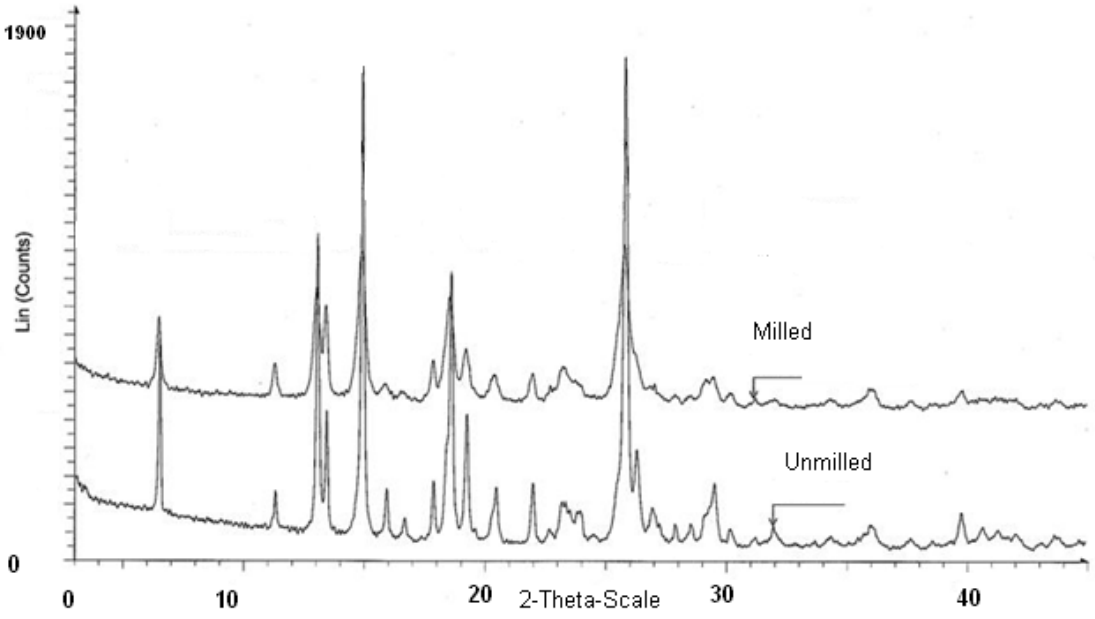


Table 4
Stability data of nanosuspension stored at different conditions.

D(0.9)nm / Zeta potential (mV)					
Initial		25 ^{0}C/60 % RH 5day		2-8 ^{0}C 5 day	
D(90) (nm)	ZP (mV)	D(90) (nm)	ZP (mV)	D(90) (nm)	ZP (mV)
397.0	-20.0	426.0	-23.9	435.0	-23.9

2. Formulation of meloxicam nanoparticulate tablet

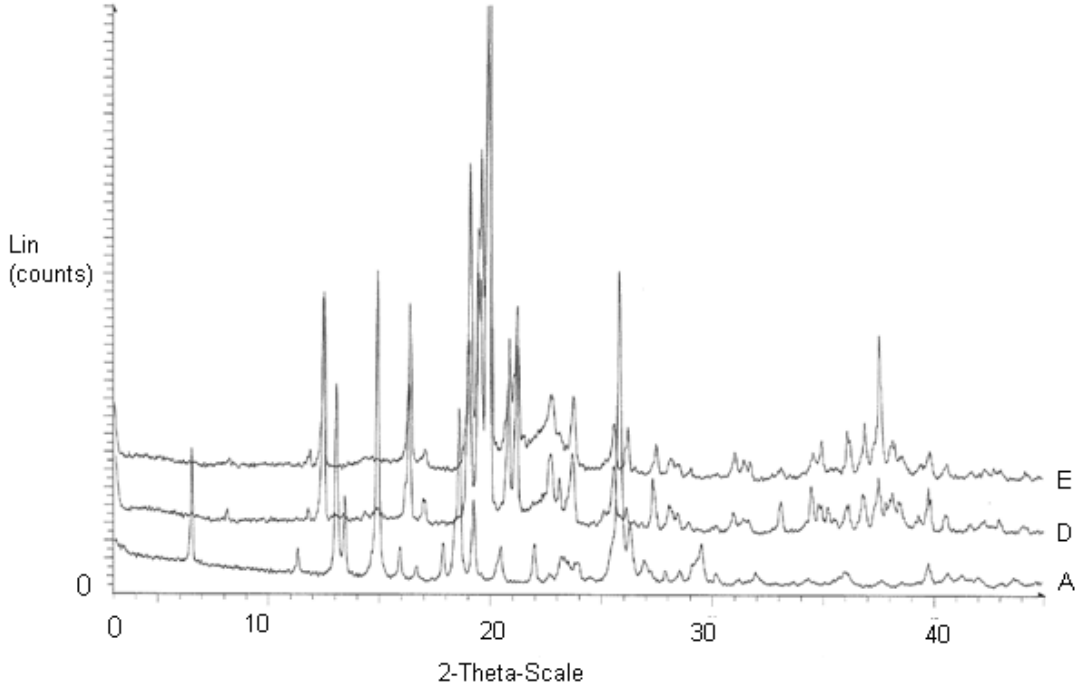
In general oral route is the first choice for the administration of drug and tablet is one of the preferred dosage forms as compared to capsule or pill. High shear wet granulation was evaluated as an approach to convert nanosuspension to solid dosage form. High shear granulation is well known for its advantages such as improved compressibility, flowability and density of the granules. The excipients used in formulations of meloxicam nanoparticulate tablets and the method of preparation was similar to the one used in formulation of reference sample Mobic® 15 mg tablet[13]. The final active blend and tablet of the meloxicam nanoparticulate composition were further evaluated with respect to their flow properties and dissolution behavior.

3. Characterization of meloxicam granules and tablets

Formulation of proper powder blend is the key factor in the production of a tablet dosage form. Formulated powder blend of two different formulations (F01 and F02) were evaluated for angle of repose, bulk density, tapped density, Compressibility index, and Hausner ratio. The granules characteristic for formulation F01 and F02 is detailed in table 5. The Angle of repose, Compressibility index, and Hausner ratio for granules of formulation number F01 and F02 showed poor to passable flow property. The tablets of both the formulation F01 and F02 were subjected to various evaluations tests such as hardness, thickness, weight variation, friability and disintegration test. These results are listed in Table 5. A major difference in hardness and thickness of both the formulation

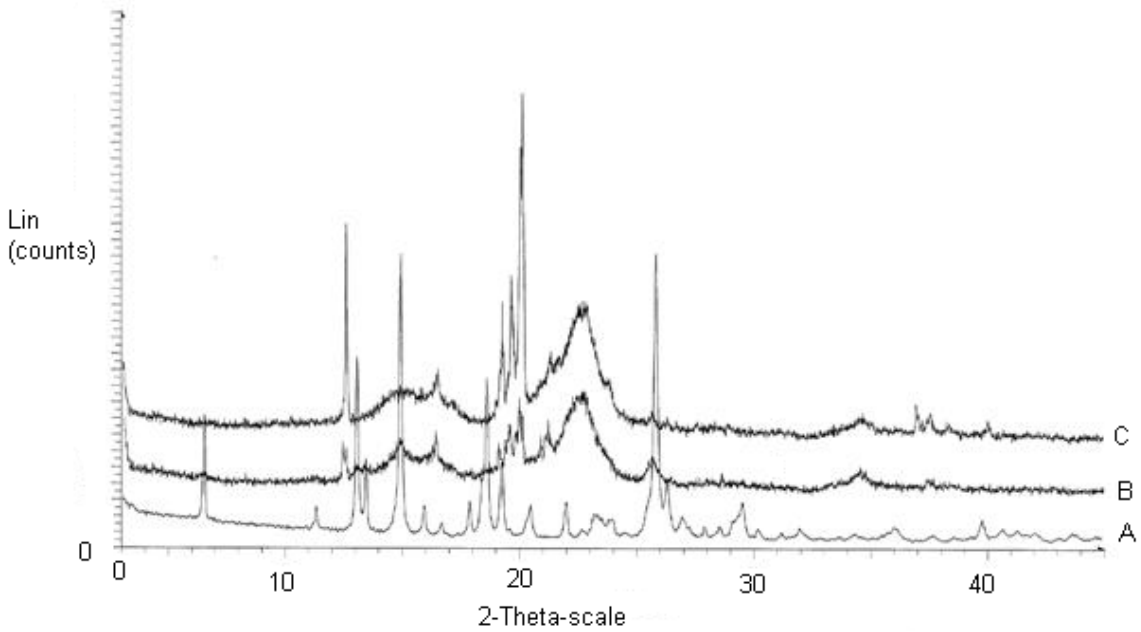
was observed. This difference is mainly because of variation in individual weight and punch tooling for both the formulations. Other properties of tablets such as weight variation and friability were well within the limit. Disintegration time for F01 and F02 were found to 60 seconds and 30 seconds respectively. This difference may be due to the larger size of F01 tablet compared to F02 which leads to decreased surface area of the tablet. Moreover formulation F02 also contains more amount of MCC which also acts as a disintegrating agent. Along with F01 and F02 reference sample of Mobic® 15 mg was also characterized for some of the parameters (Table 5). The powder X-ray diffraction study of meloxicam nanoparticulate tablet (F01 and F02) showed no significant shift in the main peaks when compared with unprocessed meloxicam. The characteristic peaks for meloxicam nanoparticulate tablets were observed at same 2ɵ value as that of unprocessed drug (Figs 2-3).

Figure 2
XRD pattern of unprocessed drug and crushed tablets of F01 meloxicam nanoparticulate and its placebo



(A) XRD pattern of meloxicam unmilled. (D) XRD pattern of F01 tablet. (E) XRD pattern of placebo tablet for F01.

Figure 3
XRD pattern of unprocessed drug and crushed tablets of F02 meloxicam nanoparticulate



(A) XRD pattern of meloxicam unmilled. (B) XRD pattern of F02 tablet. (C) XRD pattern of placebo tablet for F02.

Table 5
Evaluation of granule and tablet characteristic

Parameters	F01	F02	Marketed tablet
Angle of repose (ɵ)	34	32	-
Bulk density (g/ml)	0.477	0.416	-
Tapped density (g/ml)	0.608	0.566	-
Compressibility index (%)	21.59	26.5	-
Hausner ratio	1.275	1.36	-
Tablet wt. (mg)	700.3	373.8	180.0
Hardness (kP)	11-12	6-8	-
Thickness (mm)	6.4-6.44	5.15-5.2	2.91
Friability (%)	0.5	0.6	-
Disintegration Time (min.sec.)	01.0	00.30	03.50
Compaction force (kN)	13-14	4-5	-
Ejection force (kN)	0.12-0.14	0.022	-

Marketed tablet was characterized only for weight, thickness and disintegration time.

4. Effect of concentration of diluent on the tablet weight of meloxicam nanoparticulate composition

Two different compositions were used for formulating meloxicam nanoparticulate tablet. Formulation F01 and F02 contains lactose monohydrate and microcrystalline cellulose in a ratio of 0.8:0.2 and 0.2:0.8 respectively. The quantity of meloxicam nanosuspension required for granulation was optimized in initial screening trials (data not included in this study).The amount of binder (Meloxicam nanosuspension) required for granulation of intragranular blend of F01 and F02 was 25.6 and 50.9% respectively. The binder (meloxicam nanosuspension) uptake for granulation of formulation F02 was almost double to that required for granulation of formulation F02. This contributes mainly to the difference in the amount of MCC in both the formulations. MCC is insoluble filler. Microcrystalline cellulose has an excellent water imbibing or wicking action as compared to

lactose monohydrate. When used as a wet massing adjunct, the wicking action of MCC promotes rapid and even wetting of the powder mix. Similar observation was also made by Saigal et al.[14]Moreover when used in wet granulation it has ability to retain water, which makes the wet mass less sensitive to over wetting due to an excess of granulating fluid. Since lactose has higher water solubility a very low amount of binder is required for granulation which further leads to low water uptake. Due to the higher binder uptake property of formulation F02, the final weight of meloxicam nanoparticulate tablet was reduced almost twice to that of formulation F01.

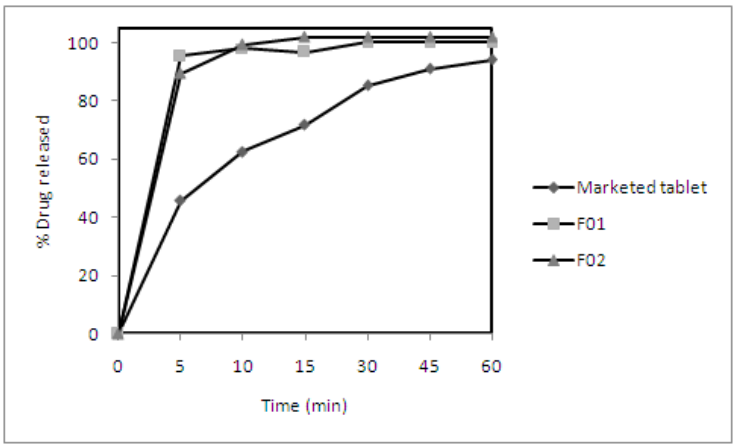
5. *Effect of particle size on the dissolution rate*

Dissolution profile for meloxicam nanoparticulate tablet against Mobic® 15 mg tablet is shown in Fig 4. Comparison of the dissolution profile obtained clearly showed a significant dissolution rate enhancement of the meloxicam from nanoparticulate composition (F01 and F02) as compared to the marketed tablet. For nanoparticulate tablet (F01 and F02), about 90.0% of the drug was dissolved within 5 minutes, whereas for marketed tablet it was just 45.7%. The decrease in particle size accompanied by increased surface area mainly yielded the increase of dissolution of meloxicam from the nanoparticulate tablet. This fact can be described by Noyes–Whitney equation[15], which states that the increase in dissolution velocity takes place in addition to the increase caused by the enlargement of the surface area.

$$\frac{dC}{dt} = \frac{DA\,(Cs-C)}{h} \qquad (3)$$

where d*C*/d*t* is the rate of dissolution of the drug particles, *D* is the diffusion coefficient of the drug in the gastrointestinal fluids, *A* is the effective surface area of the drug particles in contact with the gastrointestinal fluids, *h* is the thickness of the diffusion layer around each drug particle, *C*s is the saturation solubility of the drug in solution in the diffusion layer, and *C* is the concentration of the drug in the gastrointestinal fluids. From this equation, it is obvious that an increase in surface area leads to an increase of the dissolution rate. In addition, smaller particles of a compound also increase the saturation solubility, which further increase the dissolution rate. One can also imagine that the thickness of the dissolution layer will decrease with smaller particles [16,17,18,19], causing an increased concentration gradient.

Figure 4
Dissolution profile of meloxicam nanoparticulate tablet 15 mg against marketed tablet



6. Effect of concentration of diluent on the drug release of meloxicam from nanoparticulate composition

Additives such as diluents or fillers are often needed to maintain the tablets size of modify drug release. Inclusion of water insoluble fillers, such as MCC and dibasic calcium phosphate (DCP) are always avoided for formulating water insoluble drug, due to their property to hinder the drug release. The main reason for this is difference in mechanism of the soluble and insoluble fillers. The water soluble fillers or diluents dissolves in surrounding media, diffuses outward and decreases the tortuosity for the drugs to release. Whereas water insoluble fillers does not diffuse outward, but becomes entrapped in the matrix, consequently making drug to release difficult. An noteworthy observation is noted down in this paper. The difference in percentage drug release of formulation F01 and F02 at 5 minute time interval was not significant. Formulation F01 and F02 mainly varies with the difference in ratio of lactose to MCC, which affects the final tablet weight. Although formulation F02 contains lactose and MCC in ratio of 02: 0.8, presence of more amount of MCC didn't affect the percentage of drug release. Generally, MCC is water insoluble, and there are chances that small drug particles may get trapped between the deformed MCC particles and may delay wetting and dissolution. But presence of small amount of water soluble excipients such as lactose, acts as channelizing agent which may create pores on the tablet surface in contact of water and increases the drug release. Moreover MCC also has high water absorbing capacity which leads to faster disintegration of nanoparticulate tablet of formulation F02 as compared to F01 which may expose the nanosized drug particles to the dissolution media and enhance drug release.

CONCLUSION

Formulation of nanosuspension and its solidification both are complex processes. The complexity of nanosuspension manufacturing was resolved by selecting the formulation and process parameters from an optimization study carried out in our previous publication. The nanosuspension manufactured in the present study showed PSD d(90) and zeta potential values similar to that of the optimized formulation. The nanosuspension also showed good stability up to 5 days in 25^0 C/75%RH and 2-8^0C storage conditions. Moreover the nanosuspension didn't show any change in the crystalline form of the drug after milling which was verified by the XRD study. The meloxicam nanosuspension was converted to solid oral dosage form using high shear wet granulation. The obtained granules from formulation F01 and F02 revealed good flow characteristics. The nanoparticulate tablet of both the formulation F01 and F02, showed a significant rise in the dissolution velocity when
compared with the marketed formulation. The inclusion of soluble (lactose) or insoluble diluent (MCC) had no significant effect on the dissolution velocity. But the inclusion of more amount of insoluble diluent (MCC) in F02 tablet helped in reducing the tablet weight markedly which in turn may help in controlling the product cost and improve the patient compliance.

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